Elastin-like protein-hyaluronic acid (ELP-HA) hydrogels with decoupled mechanical and biochemical cues for cartilage regeneration.

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Public Summary:
Hyaluronic acid (HA) is a major component of cartilage extracellular matrix and is an attractive material for use as 3D injectable matrices for cartilage regeneration. While previous studies have shown the promise of HA-based hydrogels to support cell-based cartilage formation, varying HA concentration generally led to simultaneous changes in both biochemical cues and stiffness. How cells respond to the change of biochemical content of HA remains largely unknown. Here we report an adaptable elastin-like protein-hyaluronic acid (ELP-HA) hydrogel platform using dynamic covalent chemistry, which allows variation of HA concentration without affecting matrix stiffness. ELP-HA hydrogels were created through dynamic hydrazone bonds via the reaction between hydrazine-modified ELP (ELP-HYD) and aldehyde-modified HA (HA-ALD). By tuning the stoichiometric ratio of aldehyde groups to hydrazine groups while maintaining ELP-HYD concentration constant, hydrogels with variable HA concentration (1.5%, 3%, or 5%) (w/v) were fabricated with comparable stiffness. To evaluate the effects of HA concentration on cell-based cartilage regeneration, chondrocytes were encapsulated within ELP-HA hydrogels with varying HA concentration. Increasing HA concentration led to a dose-dependent increase in cartilage-marker gene expression and enhanced sGAG deposition while minimizing undesirable fibrocartilage phenotype. The use of adaptable protein hydrogels formed via dynamic covalent chemistry may be broadly applicable as 3D scaffolds with decoupled niche properties to guide other desirable cell fates and tissue repair.

Scientific Abstract:
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